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TOPIC PAPER

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The neurophysiology of female sexual function

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Abstract Recent research on the neural control of female sexual function is reviewed. The control of female genital responses has not been extensively studied and significant gaps in our knowledge remain. Sexual arousal is largely the product of spinal level reflexes. A network of interneurons processes the sensory information and generate complex patterns of activities that are then distributed to the autonomic and somatic efferents. The spinal reflexive systems are under inhibitory and excitatory control from the brainstem and hypothalamic sites. Further research is necessary to identify the mechanisms underlying female sexual function, the pathogenesis of sexual dysfunctions and their possible treatment.

Keywords Clitoris · Sexual climax · Pudendal · Pelvic · Hypogastric · Genital

The study of the neurophysiology of human female sexual function is a field still in its infancy. There remain today many important unanswered questions in this area. There have been few studies and much of what is known (or presumed to be known) is inferred from animal studies, primarily in rodents, and by analogy drawn from studies in males. The female animal studies have been predominantly focused on proceptive and receptive behaviors, such as lordosis, and few have examined the central nervous control of genital responses.

In this review, I will attempt to summarize the current state of the field. In addition, I would also like to emphasize the limitations of the data and the difficulties of drawing conclusions from studies in animals and males. Remaining questions will be highlighted and suggestions for future research will be given.

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Innervation of the pelvic organs

Motor

Comprehensive reviews of the innervation of the pelvic organs have previously been reviewed [9, 58]. Female pelvic innervation has been most extensively studied in the rat [5]. In the rat, the autonomic innervation of the pelvic organs is provided primarily by the major pelvic ganglion [70, 102, 114]. This is a compact, triangular structure located on the lateral margin of the lateral lobe of the prostate in males and the cervix in females. It is sometimes also called the paracervical ganglion [104] or the uterine cervical ganglion [5]. Both the hypogastric (sympathetic) and pelvic (parasympathetic) nerves innervate the pelvic ganglion. Postganglionic fibers from the ganglion innervate the pelvic organs, including the bladder, urethra, accessory sex glands, vagina, uterus, clitoris and penis. The largest of the nerves from the pelvic ganglion – the cavernous nerve – provides the vasodilatory innervation to the penis/clitoris [70]. The cavernous nerve is visibly smaller in the female, but otherwise the organization of these nerves is quite similar in both sexes. The vasodilation of the penis/clitoris elicited by cavernous nerve activation is mediated by the neurotransmitter nitric oxide [2, 22, 107].

Numerous studies have identified a variety of peptide neurotransmitters in sensory and motor fibers innervating the pelvic organs [28, 38, 60, 96, 101, 102, 104, 125, 136]. These peptides may act as neurotransmitters when released from motor fibers. For example, it has been determined that human vaginal blood flow and lubrication are mediated by a peptide, vasoactive intestinal polypeptide (VIP) and that the effect of VIP is diminished after menopause [56, 72, 100, 103]. When released from both motor and sensory fibers, they may

also act to modulate the sensitivity of sensory fibers to natural stimuli and the classical autonomic transmitters norepinephrine and acetylcholine. This modulation of excitability by petides has been described in the bladder [79]. It has recently been reported that sensory fibers in the skin of the penis contain receptors for melanocortin and that melanocortin IV receptor agonists induce penile erection [141]. Similar mechanisms in the female may be useful in developing drugs to treat sexual dysfunction.

Neuronal cell bodies can be labeled by the application of a tracer to the axons or terminals of a nerve. Applying tracers to the rat pelvic nerve labeled parasympathetic preganglionic neurons in the sacral parasympathetic nucleus in the lumbosacral segments of the spinal cord [51, 93]. These neurons were located in a compact column in the lateral intermediate gray matter. No differences were noted in the number or distribution of labeled cells in males or females [93].

Application of tracers to the hypogastric nerve in the rat labeled sympathetic preganglionic neurons in the thoracolumbar segments of the spinal cord [52, 94, 97]. The preganglionic neurons were found bilaterally in the intermediolateral cell column and in the dorsal commissural nucleus in the midline, dorsal to the central canal. There is little evidence yet that either the sympathetic or parasympathetic preganglionic neurons projecting to different pelvic organs are topographically organized, that is, segregated into functional groups.

The pudendal nerve innervates the striated perineal muscles, the ischiocavernosus, bulbospongiosus, external anal and urethral sphincters [20, 59, 86, 123]. The external anal and urethral sphincters are not significantly different in the two sexes, but there is a pronounced sexual dimorphism in the ischiocavernosus and bulbospongiosus muscles to the extent that these muscles are almost completely atrophied in the female rat. The pudendal motoneurons are located in the lumbar spinal cord. The number of motoneurons is sexually dimorphic, directly reflecting the dimorphism of the muscles.

Sensory

The afferent innervation of the pelvis of the female has been extensively investigated. Anatomical studies showed that sensory fibers from the pudendal, pelvic, and hypogastric nerves innervate female pelvic organs. The pudendal nerve provides sensory innervation for the perineum, clitoris, and urethra. Increased estrogen levels expand the size and sensitivity of the pudendal perineal innervation [1, 63, 65]. The pudendal sensory innervation plays an essential role in eliciting lordosis behavior [112, 113] and climax-like responses [30, 88]. The role of hormone modulation of human female pelvic sensory mechanisms is unclear.

Pelvic nerve sensory fibers innervate the vagina, cervix, or body of the uterus, with the greatest concentration in the fornix of the vagina [12, 111]. Individual fibers innervate only a single pelvic organ. Most vaginal and uterine afferent fibers appear to be unmyelinated. The vaginal and cervical innervation has been shown to be crucial for inducing pregnancy or pseudopregnancy due to mating or cervical stimulation [25, 62]. Stimulating pelvic nerve afferents in the cervix mediate the mating-induced release of lutenizing hormone and prolactin [47, 49, 130]. Chemical destruction of the unmyelinated, peptidergic sensory fibers of the cervix leads to a decreased fertility in the rat and prevention of pseudopregnancy following cervical stimulation [136, 137].

The hypogastric nerve of the rat contains relatively few axons of afferent neurons [94]. However, these neurons have been shown to be important for the pain sensation from the uterus. The majority of hypogastric afferents are unmyelinated [95]. Both the hypogastric and pelvic afferents have been shown to be modulated by hormonal factors [10, 11, 12, 117, 118].

Sensory stimuli relevant to sexual function are conveyed by afferents in the pudendal, pelvic, and hypogastric nerves, with pudendal fibers innervating the external genitalia and perigenital area, and the pelvic and hypogastric the internal pelvic organs. The afferents terminate primarily in the medial portions of the dorsal horn and in the medial central gray matter (dorsal gray commissure) of the lumbosacral spinal cord [91, 92, 86, 135]. The pudendal afferents have an almost exclusively medial distribution. Visceral pelvic afferents, on the other hand, also terminate in the lateral edge of the gray matter in the vicinity of the intermediolateral cell column, the site of the preganglionic neurons.

There is also some evidence that vagal fibers may convey sensory information from female pelvic organs to sensory nuclei in the brainstem [64, 142]. The vagal pathway remains functional after spinal cord transection and may account for the menstrual cramping, analgesia and orgasm reported in women with complete spinal cord transections [142]. Further research is necessary to determine the role of vagal sensory fibers in female sexual responses.

Interneurons

The location of interneurons relevant to sexual function have been identified by neurophysiological and anatomical studies. Stimulation of the pudendal nerve activated neurons in the medial portions of the lumbosacral spinal gray [35]. Another study also identified interneurons in the medial gray of the sacral spinal cord which responded to perineal and pelvic visceral stimulation [55]. Another technique, c-fos, has been used to identify spinal interneurons related to pelvic function. Strong activation of neurons often causes expression of the immediate early gene, c-fos, and its gene product, Fos [120]. Stimulating genital afferents resulted in labeled neurons in the medial dorsal horn, the central gray commissure, and the region of the intermediolateral cell

column, consistent with the distribution of pelvic sensory terminals. The distribution of interneurons was similar in males and females [14, 71, 115].

The use of neurotropic viruses has been used to address the question of pelvic interneurons. Viruses, such as the pseudorabies virus, are picked up by nerve terminals near the injection site, retrogradely transported to the neuronal cell body, replicated, and picked up by nerve terminals presynaptic to the infected neurons. This allows a network of synaptically linked neurons to be identified [24, 68]. After injection into the penis, clitoris, or uterus, very similar patterns of labeling were observed [81, 84, 105, 106]. The majority of labeled neurons in the spinal cord were located in the central gray region of the spinal cord and in the vicinity of the intermediolateral cell column. The majority of neurons were located in lumbosacral segments. These neurophysiological, Fos, and transneuronal techniques all indicated that pelvic and sexual reflexes are dependent on spinal neurons in the central gray region of the lumbosacral segments and that this is the spinal network that coordinates and generates sexual responses (arousal and climax). Further research on the neurochemistry of this network may provide additional pharmaceutical targets for future treatments of sexual dysfunction.

Spinal reflexes

Sexual function is based upon several spinal level reflexes, with modulation by supraspinal sites. Most identified sexual reflexes are activated by pudendal afferents. The most completely described is the bulbocavernosus reflex. This reflex is a polysynaptic response seen in males and females elicited by light touch pudendal sensory fibers. These activate pudendal motoneurons to contract the striated perineal muscles [18, 87, 116, 139]. This reflex is often used as a neurological test of the integrity of both the sensory and motor components of the pudendal nerve. Tonic stimulation of the clitoris could lead to the development of the orgasmic platform, the contraction of the levator ani and circumvaginal muscles, through the mechanism of the bulbocavernosus reflex. This reflex would also lead to contraction of the external urethral sphincter. Stimulation of the clitoris and vagina causes an inhibition of bladder activity by inhibiting pelvic nerve activity to the bladder and an increase in hypogastric nerve activity to the bladder neck, leading to detrusor inhibition and bladder neck contraction [32, 73]. These reflexes strengthen urinary continence during sexual arousal.

Stimulation of the cavernous nerve gives rise to clitoral engorgement, lengthening of the vagina, and an increase in vaginal blood flow [46, 107]. However, the reflex mechanisms involved in sexual arousal (clitoral erection, vaginal engorgement and lubrication) have not been investigated in females. It is likely that female reflex mechanisms are similar to the male. Stimulation of the pudendal nerve sensory fibers evokes long latency discharges, indicating a polysynaptic reflex, in the cavernous nerve [131] and results in increases in intracavernous pressure [13, 45]. The mechanisms underlying female sexual responses remain to be elucidated directly.

Evidence indicates that sexual climax is also a spinal level reflex. Following spinal cord injury, a significant number of women are still able to experience orgasm [128]. In anesthetized, acutely spinalized female rats, genital stimulation gives rise to a response that resembles climax in humans: rhythmic contractions of the striated perineal muscles and vaginal and uterine contractions [88]. It also includes strong activation of the cavernous nerve, driven by both hypogastric and pelvic nerve preganglionic activity. This response is neurologically very similar to the ejaculatory response seen in male rats. The activity of perineal contractions during orgasm in human males and females are also very similar [15, 16, 17].

Ascending sensory pathways

Sexual afferents terminate in the lumbar and sacral segments of the spinal cord. Sensory information is relayed to supraspinal sites via both spinothalamic and spinoreticular pathways. The spinothalamic pathways primarily convey the fastest fibers related to the encapsulated nerve endings of the phallus [23, 66]. They travel in the dorsal columns and consist primarily of fast myelinated fibers [23]. These fibers terminate in the posterolateral nucleus of the thalamus and subsequently relayed to the medial thalamus. Spinoreticular fibers tend to be slower than the spinothalamic fibers. They travel in the contralateral (and, to a lesser extent, ipsilateral) lateral spinal columns and terminate in brainstem reticular formation. There is evidence that vagal fibers may also convey sensory information from female pelvic structures to sensory nuclei in the brainstem and may be capable of mediating sexual responses in women with spinal cord injuries [64].

Studies in humans have examined cortical-evoked potentials following electrical stimulation of the dorsal nerve of the penis/clitoris (a division of the pudendal nerve). Evoked potentials are recorded bilaterally from cortical areas, with the highest amplitude in the midline (Cz-2) over the sensory cortex [44, 48]. This distribution is consistent with pudendal representation deep in the midline interhemispheric fissure in humans [109] and cats [19]. The amplitudes of cortical evoked responses are larger in men than in women [50], although slightly shorter in latency in women [99]. The smaller size in women may be related to fewer fibers innervating the clitoris relative to the penis or to the greater accessibility of stimulation of the male dorsal nerve.

Studies in children (3–13 years old) revealed that the cortical evoked potentials from the phallus shorten in latency with maturation and show a narrower volley [110]. These results indicate that the nerve conduction velocity of central nervous system (CNS) perineal sen-

sory pathways increases and shows a greater uniformity with maturation. However, these changes were gradual and did not show abrupt changes around puberty. No major differences were reported between boys and girls. This is another confirmation that the organization of neural pathways involved in sexual function is fundamentally similar in males and females.

Supraspinal nuclei

Spinal sexual reflexes have long been known to be under descending control from brainstem sites [7]. One site has been identified in males as important in inhibitory control of climax-like responses. Given the high degree of similarity of this climax-like response between males and females, it is highly likely that this region plays a similar role in females. Neurons in the nucleus paragigantocellularis receive genital sensory information in males and females [57, 119]. The nucleus paragigantocellularis projects directly to pelvic efferent neurons and interneurons in the lumbosacral spinal cord [82]. Neurons in this area are transneuronally labeled following virus injection into the penis [84] and the clitoris [81]. Lesions of this nucleus are as effective as spinal transection in suppressing a tonic inhibition of the climax-like response [82]. Most of the neurons in this region stain positively for the neurotransmitter serotonin and serotonin applied to the spinal cord inhibits spinal sexual reflexes [83]. This is a likely candidate for mediating the high incidence of orgasmic dysfunction seen with the use of selective serotonin reuptake inhibitor (SSRI) antidepressants, which elevate brain serotonin levels [69, 90]. Identification of the serotonergic receptor subtype mediating the inhibition could leads to newer antidepressants without adverse sexual side effects and to treatments of sexual dysfunction caused by excessive inhibitory tone.

The nucleus paragigantocellularis has been implicated in several functions, such as the modulation of pain [4], cardiovascular control [21, 75, 78], as a relay in the defense reaction [80], and respiratory control [36]. In addition, the nucleus paragigantocellularis is a prominent input to the locus ceruleus [3]. These findings indicate that the role of this region is not necessarily specifically involved in sexual function, but may be involved in determining spinal excitability appropriate to the behavioral and homeostatic state of the animal [85].

Several other sites have been anatomically identified for their projections to lumbosacral spinal cord, but their functional role in sexual response is unknown. The lumbosacral spinal cord receives strong projections from other serotonergic nuclei in the brainstem, the raphe nuclei pallidus, magnus and parapyramidal region [54, 75]. There are also significant noradrenergic projections from the A5 catecholaminergic cell group and from locus ceruleus [76, 98]. These provide a dense innervation of pudendal motoneurons and other lumbosacral targets [61, 124]. Future research is needed to identify the functional significance of these projections and whether adrenergic drugs could be used to treat sexual dysfunction.

In conventional and viral tracing studies, a projection from Barrington's nucleus in the parabrachial region of the pons to lumbosacral cord has been identified [54, 77, 81, 106]. This region has long been known to play a role in micturition [6, 67]. It has also been implicated in pelvic contractions related to defecation and parturition [39, 40, 41, 42, 43]. Its role in sexual responses has yet to be investigated, but it is likely that it participates in controlling the pelvic musculature. Future research could be of value in developing treatment for disorders of pelvic muscle tone, such as stress incontinence.

In the midbrain, the periaqueductal gray is known to be an important relay center for a variety of homeostatic functions and motivated behaviors, including sexual function. It has extensive connections with all of the brainstem sites just discussed and has connections with many hypothalamic sites involved in sexual function [8]. Neurons in this area are labeled following viral injection into the clitoris and uterus [81, 106]. The great majority of these neurons in this region are activated during copulatory behavior [119].

The hypothalamus is an essential site for reproduction and sexual behavior, as well as for a very large number of homeostatic and motivated behaviors [133]. The medial preoptic area has long been known to play a role in controlling male sexual behavior. Lesions of this region severely attenuate or abolish male copulatory behavior in every species tested [89]. However, medial preoptic lesions do not abolish erections caused by sleep [122], exposure to volatile odors from estrus females [74], or masturbation [129]. Medial preoptic lesions do not decrease sexual motivation [34]. In the male, it appears likely that the medial preoptic area does not generate sexual arousal or behavior, but is involved in the animal's ability to recognize a sexual partner. A similar conclusion may be true in the female. Lesions of the medial preoptic region in female rats resulted in greater display of lordosis but, when given the option, females avoided male partners. A tentative conclusion is that, in both sexes, the medial preoptic is not directly involved in sexual motivation or performance but with mate selection.

The paraventricular nucleus of the hypothalamus is a likely candidate for control of genital responses. It is known that during sexual arousal and orgasm, oxytocin from the paraventricular nucleus is secreted from the posterior pituitary into the blood stream in male and female humans [26, 27]. There is a direct projection from the paraventricular nucleus to the autonomic outflow from multiple segments, as well as direct projections to pelvic autonomic and somatic efferents [29, 121, 140]. The paraventricular nucleus is extensively connected with the medial preoptic area [126, 127]. The paraventricular nucleus was consistently labeled after pseudorabies virus injection into the clitoris and uterus [81, 106]. Neurons in the paraventricular nucleus are activated during copulation in female rats [37] Further studies, such as stimulation studies and oxytocin phar-

macological studies, are needed to further characterize the sexual role in females of the paraventricular nucleus.

Forebrain regions involved in female sexual function have largely been identified on the basis of Fos staining in copulatory tests and viral staining. Medial amygdala, bed nucleus of the stria terminalis, and some other regions are most consistently identified [31, 33, 106, 134, 138]. The Fos labeling in these regions is strongly affected by vaginocervical stimulation during copulation. The medial amygdala is believed to be involved in controlling sexual motivation in the male [89]. Similar conclusions in the female can not currently be drawn. Considering that hypoactive sexual drive in women is a common sexual dysfunction, this question is of strong clinical importance.

In one series of methodologically flawed studies, intracranial stimulation of male and female patients suffering from severe psychiatric disorders and/or brain damage, elicited subjective pleasurable response, which were described as sexual in nature and in some cases were associated with reports of orgasm [53]. An area consistently associated with this response was the septal region. Electrical stimulation or stimulation with cholinergic and adrenergic agents were effective. A functional imaging study in women identified cortical sites associated with visually-evoked sexual stimulation [108]. Sexual arousal was associated with an increased activity in inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobe. This is generally consistent with brain activation seen with sexual arousal in men [132].

Organizing principles

The control of sexual function is based upon spinal mechanisms. The spinal cord provides the autonomic and somatic innervation of the sexual organs. Sensory information from the sexual organs project to interneurons in the lower spinal cord. These interneurons likely generate the coordinated activity of sexual responses. The spinal reflex mechanisms are under inhibitory and excitatory control from supraspinal nuclei. These nuclei are highly interconnected. Many of them also receive genital sensory information. It is likely that during sexual activity, sensory activation of supraspinal sites causes a decrease in the inhibition, and an increase in the excitation of the spinal reflexive mechanisms by the supraspinal sites. Higher order sensory and cognitive processes likely modulate the activity of supraspinal nuclei controlling sexual function.

Conclusions

There remain large gaps in our understanding of the central nervous control of female sexual function. This problem is especially acute with regard to higher centers. Most of the animal work relates to receptive behavior in female animals and very little on the control of genital responses. There is considerably more research on these issues in males. It is likely that there will be significant homology between males and females in the control of sexual function. However, significant differences may also be present, especially in forebrain regions. Therefore, it is unwise to assume a complete correspondence between the male and female and to try to construct a neural wiring diagram of the female based largely on research in the male. Obviously, there is a tremendous need for more research in this area.

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